nostic. The electrocardiogram is characteristically normal, and signs of pericardial injury are conspicuous by their absence, unless there is an infectious cause as in pyopneumopericardium.

The recognition of pneumopericardium in the presence of a history consistent with pericarditis, but with a normal electrocardiogram and characteristic findings on a roentgenogram of the chest, is important since the management and prognosis is dependent upon the underlying disease state as mentioned above. In the absence of any obvious underlying cause, a history of recent exertion, especially that involving a Valsalva maneuver, should be sought. Mistaking this presentation for pericarditis would lead to an error in therapy, since such cases of spontaneous or idiopathic pneumopericardium are usually associated with small amounts of air and have an excellent prognosis with conservative management.

Summary

Pneumopericardium is an uncommon entity with numerous possible causes. Clinically it often presents with pericarditis. Its spontaneous occurrence following prolonged Valsalva maneuvers is associated with a benign clinical course. In otherwise healthy patients presenting with pericarditis, proper recognition of this condition and its classic radiologic findings may prevent unnecessary therapy.

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Histiocytic Medullary Reticulosis with Central Nervous System Involvement

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HISTIOCYTIC MEDULLARY RETICULOSIS (HMR) is a malignant disorder of proliferating histiocytes characterized by a rapidly progressive and fatal course of fever, wasting, generalized lymphadenopathy, hepatosplenomegaly and pancytopenia. It was first described in 1939 by Scott and Robb-Smith,[1] who distinguished it from other malignant lymphoreticular diseases by characteristic morphologic features in lymph node and spleen. This entity has been further characterized immunologically as a malignant proliferation of the M-cell lineage (monocyte-macrophage-histiocyte).[2]

Central nervous system involvement in HMR is rare,[3] reported only in isolated cases.[4] The following case report describes a patient with HMR in whom antemortem manifestations of neurologic dysfunction and extensive pathologic involvement of the central nervous system were present.

Report of a Case

A 44-year-old woman was admitted to hospital at Santa Clara Valley Medical Center in October of 1972 for the evaluation of progressive lethargy, anorexia, abdominal discomfort, chills and fever, and weight loss occurring insidiously over four months. Four weeks before admission, episodic temporal headaches developed, followed by lightheadedness. On initial physical examination, the patient appeared ill, with moderate hepatosplenomegaly, mild ascites and wasted extremities.

Laboratory studies gave the following values: hematocrit reading, 36 percent; hemoglobin, 11.1 grams per 100 ml; leukocyte count, 3,800 per cu mm, with 51 percent neutrophils, 4 percent band

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forms, 28 percent lymphocytes (a few atypical) and 12 percent monocytes. The red cells were hypochromic with pronounced microcytosis, and the reticulocytes were 4.5 percent. Serum iron concentration was 117 μg per 100 ml (normal: 65 to 145); binding capacity, 212 μg per 100 ml (normal: 260 to 425). Results of bone marrow biopsy and aspirate studies showed erythroid hyperplasia. The platelets were 235,000 per cu mm; the prothrombin time was 70 percent. Alkaline phosphatase value was 5.1 Bodansky units (normal: 1 to 4.5); lactic dehydrogenase, 1,260 Burger-Broida units (normal: 100 to 350), and total bilirubin, 0.9 mg per 100 ml (normal 0.2 to 1.2). On serum protein electrophoresis, total protein was 5.1 grams per 100 ml (normal: 6.2 to 8.5); albumin, 2.2 grams per 100 ml (normal: 3.5 to 4.5) and the pattern unremarkable. Immunoelectrophoresis showed decreased gamma G and gamma M fractions. Cultures and serologic tests for bacteria, fungi and viruses were negative.

In November 1972 hepatosplenomegaly and grossly normal lymph nodes were noted on laparotomy. The spleen was found to weigh 600 grams with congestion and histiocytic infiltration of the red pulp. No significant abnormality of the liver was seen. Atypical histiocytic proliferation with a sinusoidal pattern was noted in a paraaortic lymph node. Findings on studies of bone marrow showed erythroid hyperplasia. The diagnostic impression at discharge was occult malignancy.

During the next 3½ months, fever, lethargy, anorexia and weight loss persisted. Bilateral leg pain became more severe. Findings on a gastrocnemius muscle biopsy study showed myopathy with necrotic muscle fibers. On readmission of the patient for intense lower extremity pain (March 1973), examination showed persistent, moderate hepatomegaly and pronounced pitting edema, distal hypalgesia and hyporeflexia in the lower extremities. During the stay in hospital, episodic confusion, agitation and inappropriate responses to questioning, with an inability to name objects, were noted. On brain scan, an area of faint uptake in the left frontoparietal region was seen and this was substantiated on two subsequent studies. Cerebral angiography gave normal findings. An electroencephalogram showed diffuse cerebral dysfunction of a nonspecific type. On three occasions results of studies of cerebrospinal fluid showed protein levels in the range 110 to 150 mg per 100 ml (normal: 10 to 45); glucose, 55 mg per 100 ml (normal: 40 to 70); 1 to 5 leukocytes per cu mm and no malignant cells. Therapy with prednisone, 60 mg per day, was begun on May 13. Findings on lymphangiography suggested an enlarged paraaortic lymph node, and a biopsy study during laparotomy, June 1973, showed infiltration of the subcapsular sinuses by undifferentiated malignant cells, retrospectively interpreted as histiocytic medullary reticulosis. A sinusoidal and periportal infiltrate of atypical histiocytes was observed in the liver. Cyclophosphamide, 100 mg per day, was added to the treatment regimen on June 14 and was well tolerated without evidence of toxicity.

Mentation continued to deteriorate. The final admission, August 1973, was prompted by a symmetrical tonic-clonic seizure episode with deviation of the head and eyes to the left and postictal obtundation. Findings on neurologic exami-

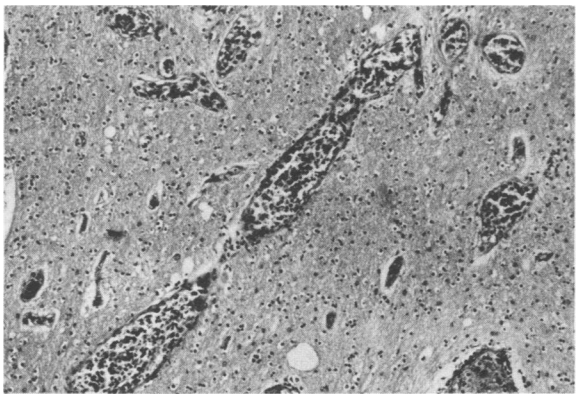

Figure 1.—Malignant histiocytes confined within the lumina of vessels of the subcortical white matter in the hippocampal gyrus. (Hematoxylin-eosin, reduced from original magnification 100×).

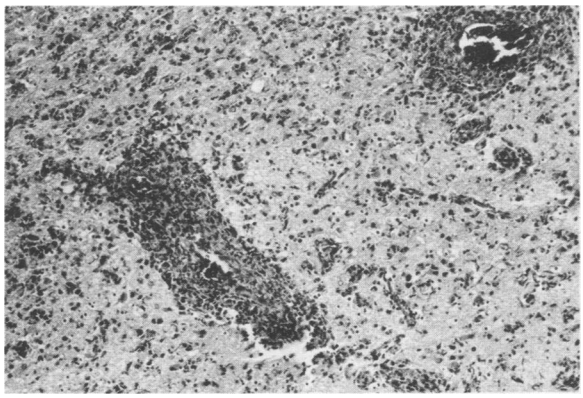

Figure 2.—Perivascular spaces with malignant histiocytes and infiltration of surrounding thalamic neuropil (Hematoxylin-eosin, reduced from original magnification 100×).

nation showed anisocoria with right fixed pupillary dilatation. Lumbar puncture yielded clear cerebrospinal fluid with a protein content of 190 mg per 100 ml, and nonmalignant cells. No abnormalities were shown on brain scan. Progressive unresponsiveness ensued, and the patient died on August 21, 1973 after 14 months of illness.

Necropsy

At necropsy, malignant histiocytes were found to be present in lymph nodes, kidney, bladder, heart, lungs and bone marrow. The proliferating malignant histiocytes were large, pleomorphic and atypical. The nuclei were large with variably fine to coarsely-clumped chromatin, prominent nucleoli and an irregular membrane. Cell borders were indistinct, and the cytoplasm was abundant, pale, blue-gray to pink and vacuolated. Erythrophagocytosis was observed in scattered cells.

Peripancreatic and paraaortic lymph nodes were small, firm, yellow-tan in color and 4 to 6 mm in average diameter. Aggregates of malignant histiocytes occupied the subcapsular and medullary sinuses without effacement of the nodal architecture.

The right and left kidneys weighed 250 and 320 grams, respectively, and were unremarkable on gross examination. Viewed microscopically, capillaries of scattered glomerular tufts and peritubular networks were engorged with malignant histiocytes. Similar intravascular aggregates were found in the bladder, heart and lungs. The bone marrow was focally infiltrated with malignant histiocytes.

Study of the 2,600 gram liver showed atypical histiocytes in the sinusoids. The skin, gastrointestinal tract and pancreas were found to contain intravascular collections of atypical histiocytes.

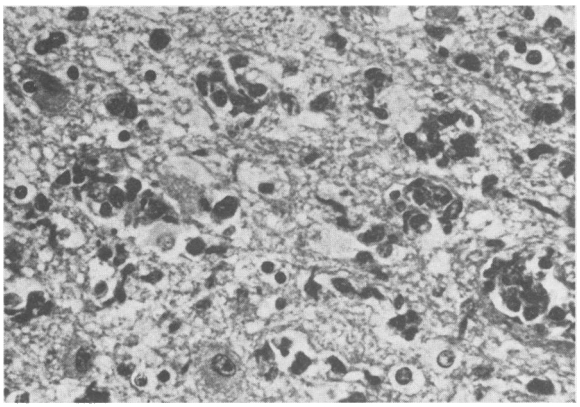

Figure 3.—Infiltrate of malignant histiocytes, pleomorphic microglia and reactive astrocytes in thalamic parenchyma (Hematoxylin-eosin, reduced from original magnification 400×).

Neuropathology

The fresh brain weighed 1,100 grams. The external configuration of the brain was unremarkable. Coronal sectioning after 10 percent formalin fixation disclosed multiple, scattered areas of cortical thinning with focal linear necrosis most prominent in the parietooccipital region. A circumscribed area of blue plexiform discoloration, 0.5 cm in diameter, was located in the subcortical white matter of the right frontal pole. The basal ganglia, cerebellum and brainstem were unremarkable on gross examination.

On microscopic examination, neoplastic infiltration was extensive. Dense clusters of malignant histiocytic cells, with morphologic features similar to those described in other organs, occupied the lumina of medium and small vessels (Figure 1). These cells in many instances infiltrated the vessel walls, distending the perivascular space, and in some areas diffusely infiltrated the surrounding brain (Figure 2). In many small vessels, the cells were present only in the perivascular spaces. In the parenchyma, many cells assumed a more elongated, flattened, twisted, bizarre appearance and intermingled with cells identifiable as pleomorphic microglia. Mitoses were moderately frequent and erythrophagocytosis was occasionally present. Reactive astrocytosis was present at the periphery of areas of involvement (Figure 3). In some regions of the frontal cortex cellular infiltration involved the subpial regions and overlying subarachnoid space. Elsewhere, tumor cells were confined within the lumina of leptomeningeal vessels. Reticulin stains showed increased concentric, perivascular, reticulin fibers investing small groups of tumor cells. Tumor involvement was extensive in the frontal cortex, thalamus and internal capsule and more focal in the putamen, globus pallidus, hypothalamus and temporal lobe. The discolored area in the right frontal white matter showed telangiectasia with thin-walled, endothelial lined spaces distended with malignant histiocytes. Diffuse vascular, perivascular and parenchymatous involvement was present in the midbrain tectum, periaqueductal gray matter, substantia nigra and cerebral peduncles. The floor of the fourth ventricle in the upper pons was also involved while in the basis pontis and medulla, malignant cellular aggregates were confined within

blood vessels. In the cerebellum, there was local infiltration of white matter and dentate nucleus.

The grossly visible cerebral cortical lesions represented pseudolaminar necrosis characteristic of an anoxic episode occurring several weeks before death. Focal areas of patchy Purkinje cell loss and proliferation of Bergmann's glia characterized the anoxic process in the cerebellum. (The case was reviewed by Drs. Lucien J. Rubinstein and Roger Warnke, Department of Pathology, Stanford University, who substantiated the diagnosis.)

Discussion

Histiocytic medullary reticulosis is a systemic proliferation of malignant histiocytes occurring predominantly in the lymph nodes, spleen and bone marrow. In lymph nodes the proliferating cells permeate the subcapsular and medullary sinuses, generally preserving or only partially distorting the nodal architecture. In the spleen the proliferation tends to occur in the red pulp sinuses, with partial obliteration of the white pulp. Hepatic involvement is sinusoidal and periportal. The neoplastic histiocytes have variable nuclear pleomorphism, prominent nucleoli and abundant pale cytoplasm with phagocytic material including erythrocytes. The clinical course is relentless and ultimately fatal, and the response to treatment disappointing.[5,6]

The pattern of lymph node involvement in this case is characteristic of histiocytic medullary reticulosis. Although the histiocytic infiltrate in the splenic red pulp is atypical and not cytologically malignant, a diagnosis of histiocytic medullary reticulosis is still tenable since cases have been observed without cytologically malignant histiocytes in the spleen. The deceptively bland appearance of the histiocytic infiltrates not only makes the distinction from a reactive process difficult,[7,8] but also accounts for the frequent inability to diagnose the disease antemortem.[5]

The unusual feature here is the extensive infiltration of the central nervous system. Other lymphoreticular neoplasms can involve the brain either primarily (reticulum cell sarcoma-microglioma) or as a manifestation of systemic disease.[9-11] In the latter instance, dural and leptomeningeal infiltration occur most commonly, although brain parenchyma occasionally can be involved,[10,12,13] producing a morphologic pattern similar to this case of histiocytic medullary reticulosis.

In contrast to the scarcity of documentation of central nervous system involvement in histiocytic medullary reticulosis is the relatively frequent occurrence of brain involvement in an uncommon, familial, lymphoreticular disorder of infancy and early childhood, designated "familial hemophagocytic reticulosis."[3,14-16] The clinical characteristics, except for age and familial occurrence, are similar to histiocytic medullary reticulosis, and histiologic features are identical.[17,18] The relationship of these separately described disease entities, as well as other disorders of proliferating histiocytes, remains to be elucidated by evolving concepts of pathogenesis and nosology.[19,20]

Summary

In a 44-year-old woman persistent fever, weight loss, hepatosplenomegaly, and neurologic symptoms and signs developed. The characteristic morphology of histiocytic medullary reticulosis in lymph nodes was shown at autopsy. Involvement by malignant histiocytes occurred in many organs, including the brain, where parenchymal infiltration was extensive. The clinical, general pathological and neuropathological features of this unusual occurrence are presented, and the relationship to familial hemophagocytic reticulosis is discussed.

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